and the reasons why the invention would not be obvious to those of ordinary skill in the art. In particular, Dr. Phipps points out that it is important to recognize that fentanyl is an extremely potent analgesic that is approximately 100 times stronger than morphine and 5-10 times stronger than hydromorphone with sufentanil being even more potent. He further explains that with such potent drugs that require only microgram quantities, there is always the danger of overdoses. He therefore initially points out that an electrotransport system for delivery of those potent substances must provide safe transdermal administration.

To support this point, Dr. Phipps explains that it was well known that diffusion of fentanyl and sufentanil substances through the skin was possible without the application of current, especially if the system were inadvertently applied to a skin site with a compromised barrier function (e.g., a skin surface that has been abraded, scratched, sunburned, etc.). He further states that it was also well known that the rate of diffusion of a substance across the skin could be decreased by decreasing the drug concentration. Dr. Phipps therefore concludes that low concentrations have been desired to minimize diffusion (i.e., passive delivery) when an electrotransport device is not transmitting current to the skin. He also notes that it is desired that the donor reservoir contain only the amount of drug needed for treatment of the patient to minimize the potential for inadvertent misuse or abuse of a "used" system. As evidence that the prior art does not teach the invention, the Declaration provides a copy of the article by R. V. Padmanabhan et al entitled "*In Vitro* and *In Vivo* Evaluation of Transdermal Iontophoretic Delivery of Hydromorphone." The article describes experiments involving the iontophoretic delivery

of hydromorphone hydrochloride and indicates the delivery rate was independent of the concentration of hydromorphone in the donor solution over the range from 0.01M to 0.8M and states on page 130:

> Total depletion of the donor compartment should have occurred in approximately 18 hours, therefore the steady-state delivery of hydromorphone through pig skin was not significantly influenced until the donor solution concentration had dropped to about one millimolar.

Dr. Phipps identifies a further article which provides a case example that confirms the general understanding that for a primarily aqueous transport pathway through skin without competing ions in the donor reservoir, the efficiency of drug delivery is independent of drug concentration.

Such teachings in the art would certainly not lead to the present invention and would actually lead those skilled in the art away from the invention as defined in the claims of record. Indeed, it is pointed out that Example 1 of Phipps et al, U.S. Patent No. 5,423,739, and Experiment 1 of Phipps et al, U.S. Patent No. 5,125,894, describe the administration of hydromorphone with Experiment 3 describing results similar to those set forth in the Padmanabhan et al article.

In significant contrast to the teachings in the art, Dr. Phipps has found that the claimed concentrations of fentanyl and sufentanil in the donor reservoir are needed in order to achieve a drug flux that is independent of concentration at a given current. Moreover, rather than having a donor reservoir that is designed to be fully depleted when administration is completed, the present invention requires the concentration to be maintained substantially throughout the delivery period which means that administration is terminated even though a substantial amount of the drug still remains in the reservoir.

This latter feature is contrary to the general understanding in the art to design donor reservoirs so that they are substantially depleted of drug at the completion of the administration period.

Without improper reference to the present application, those of ordinary skill in the art would not arrive at the claimed invention from the combined teachings of the prior art. In particular, the aforementioned Phipps et al, U.S. Patent No. 5,423,739, relates to a device and method for iontophoretic drug delivery. While fentanyl and sufentanil are identified as possible active agents, they are but two materials in a lengthy list that extends over columns 13 and 14 of the patent and neither of these materials are included in the patent examples. Indeed, there is absolutely nothing in the '739 patent which would lead one of ordinary skill in the art to the present invention. As pointed out above, hydromorphone is exemplified and, with the understanding provided by the Padmanabhan et al article, one would be led to the understanding that hydromorphone could be used at virtually any concentration and could be depleted to substantial exhaustion in the donor reservoir. This certainly would not lead to the present invention and, if anything, would lead one of ordinary skill in the art directly away from the present invention.

The aforementioned Phipps et al, U.S. Patent No. 5,125,894, is similarly deficient. While the general effect set forth at column 11, lines 8-16 is known, those skilled in the art would not be led to the specific levels defined in the claims and would certainly not be led to maintaining the defined levels of fentanyl salt of sufentanil salt (which are again higher than what one would believe appropriate for such potent drugs)

substantially throughout the analgesic drug electrotransport delivery period wherein the analgesic drug is delivered through the body surface. This is particularly true in view of the specific teachings in the Padmanabhan et al article which teaches one skilled in the art that hydromorphone, a drug specifically illustrated in the '894 patent can maintain a constant flux for a given current down to about one millimolar. Accordingly, the '894 patent also does not teach the concentration levels of the defined fentanyl and sufentanil salts set forth in the claims. In this respect, it is pointed out that a reference that gives only general guidance, and is not at all specific as to the particular form of the claimed invention and how to achieve it, may make a certain approach obvious to try, but does not make invention obvious, Ex parte Obukowicz, 27 USPQ2d 1063 (BPAI 1993).

The Examiner's reliance on the combination of Weaver et al, U.S. Patent No. 5,019,034, Sibalis et al, U.S. Patent No. 4,878,892, and Levy et al, U.S. Patent No. 4,822,802, is also believed to be improper. Neither Weaver et al nor Sibalis et al in any way relate to the electrotransport of fentanyl salt of sufentanil salt. Indeed, Sibalis et al specifically relates to the electrolytic transdermal delivery of polypeptides which the patent itself distinguishes from the delivery of other materials in the passage at column 1, lines 26-50. Such contrasting information in the references themselves cannot be ignored in assessing the patentability of the present invention.[1]

While Levy et al does describe the transdermal administration of fentanyl and sufentanil, the patent relates to a passive transdermal system which is significantly

[1] See, e.g., In re Dow Chemical, 5 USPQ2d 1529 (Fed. Cir. 1988) wherein the court held that evidence that supports, rather than negates, patentability must be fairly considered.

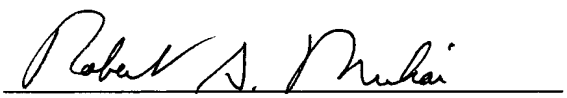
different from electrotransport systems. Indeed, as pointed out by Dr. Phipps, one would generally seek lower donor reservoir concentrations in an electrotransport device to prevent passive delivery when the device is not activated. Hence, even if there existed some proper basis for combining the teachings of the different patents, one would still not obtain the presently claimed invention, particularly since there is not one teaching which would lead to an appreciation of the high concentrations of the named potent drugs set forth in the claims and the fact that there are ample reasons why one would not use such concentrations.

For the reasons provided above and in view of the evidence of record including the attached Declaration, applicant respectfully submits that the presently claimed invention is neither anticipated nor suggested by the cited prior art. Accordingly, reconsideration and allowance of the present application are requested.

Should the Examiner wish to discuss any aspect of the present application, he is invited to contact the undersigned attorney at the number provided below.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 

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